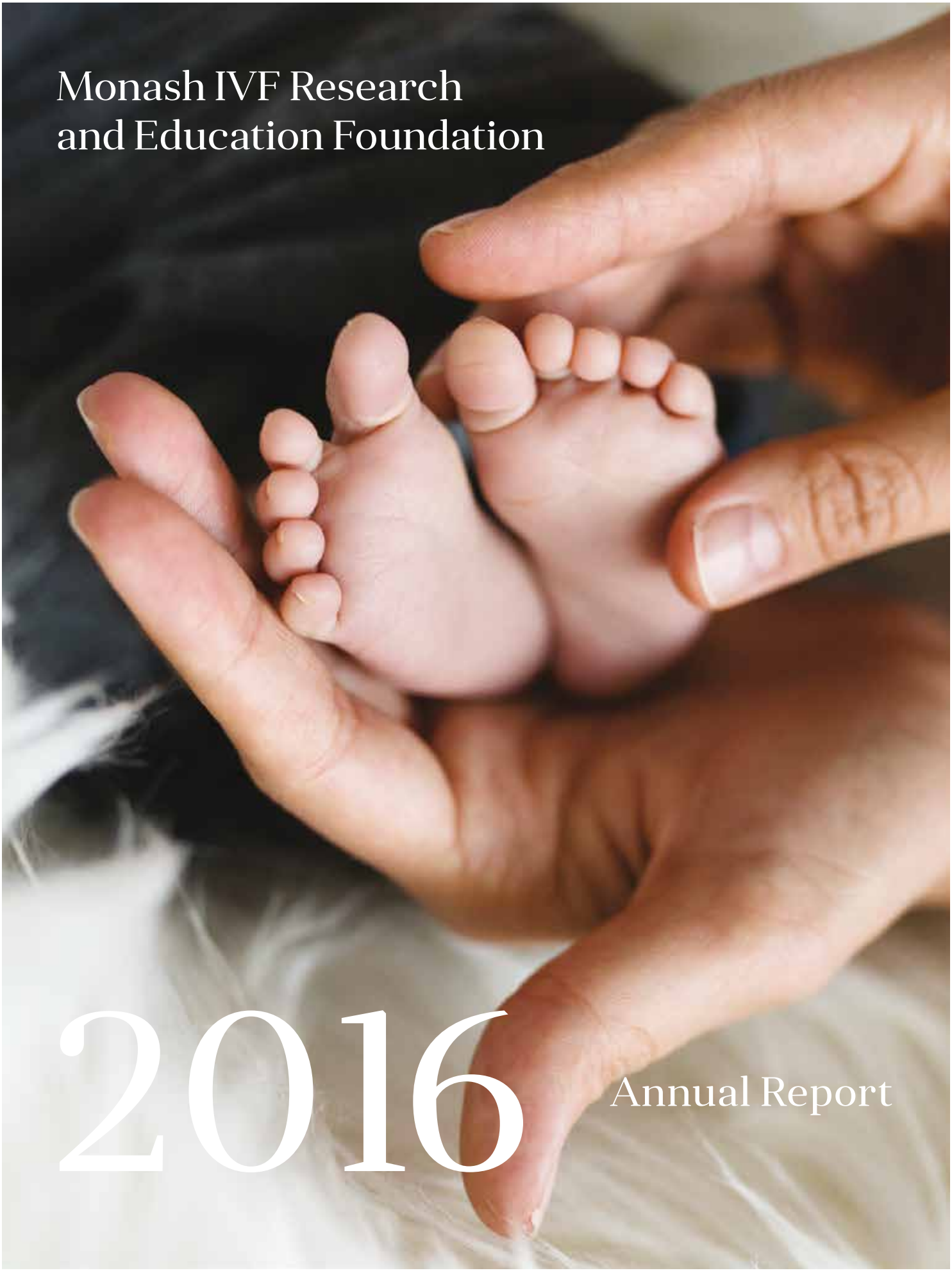
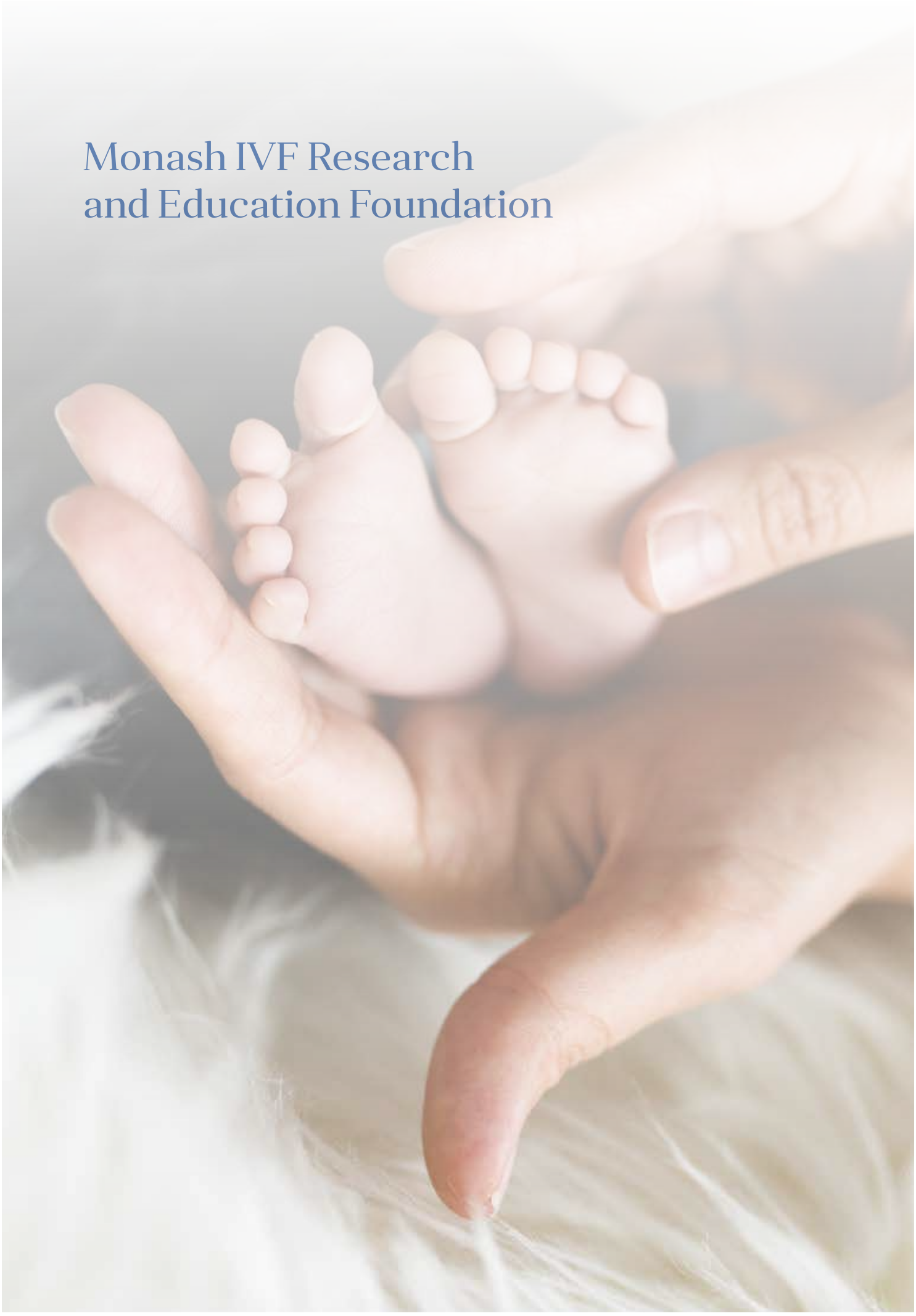
MONASH IVF GROUP



Monash IVF Research and Education Foundation

2016 Annual Report

Monash IVF Research and Education Foundation



Contents

The Monash IVF Group continues to recognise the close linkage between research and best clinical practice and therefore remains very active in translational research and postgraduate medical education in reproductive medicine.

Excellence in Research and Education

Monash IVF Research and Education Foundation (MREF)

Since 2009, the Monash IVF Research and Education Foundation (MREF) has functioned as a subcommittee of the Medical Advisory Committee (MAC) and relies upon a committed team of researchers and educators. The MREF advises the MAC, and thence the Monash IVF Group Board, on ways in which the Group can conduct internationally-recognised research, provide educational programs for health professionals and raise community awareness and knowledge in reproductive medicine.

The MREF maintains its historical relationship with Monash University and its affiliated institutes. A senior University member is on the MREF Advisory Board, and many senior Monash IVF staff hold adjunct academic appointments and are involved in joint postgraduate educational programs.

MREF supports studies that focus on the effectiveness and safety of ART treatments and the best outcomes for couples and their offspring. Major recipients of the research funding include investigators at the Monash University Departments of Obstetrics and Gynaecology, the School of Biological Sciences, and the Hudson Institute of Medical Research and the Murdoch Institute.

Joint educational activities are undertaken with the University's Education Program in Reproductive Biology (EPRD) including participation in EPRD's renowned reproductive science courses, along with specialized courses for postgraduate medical education for local and overseas clinicians. Recognizing the key roles of embryology, nursing and allied staff to the success of our assisted reproductive treatment program, innovative educational programs have also been developed for these groups.

With the formation of the Monash IVF Group in June 2014, the research skills and resources of the Repromed program and its affiliates at the University of Adelaide, has broadened the opportunities for research. An Executive of MREF and the Repromed research team sets Group-wide research and development objectives, to ensure increasing collaboration and the optimal use of resources, particularly in clinical trials aiming to improve success rates. The Monash Ultrasound for Women team is also integral to MREF and has an active research programme in reproductive imaging.

This report includes the research and educational outputs from MREF Advisory Board members and other Monash IVF Group staff in regard to their work both at Monash IVF and within their professional spheres, in the field of reproductive medicine and fertility control over the 2016 calendar year.

Comment from the Group CEO (on behalf of the Board)

James Thiedeman | Monash IVF Group Chief Executive Officer

At the heart of Monash IVF Group is a commitment to delivering world class care to patients across our fertility and women's imaging services. Today we have a footprint of over 40 IVF clinics, ultrasound practices and service centres across Australia and Malaysia.

Our network includes over 100 dedicated doctors, and more than 700 scientific, nursing, allied health and support staff – many of the best minds in the health care sector. We are exceptionally proud of the pregnancy rates and clinical outcomes we deliver across our clinics and it is incumbent upon us to continually strive for improvement. Through the Monash IVF Research and Education Foundation (MREF), we have a platform to continue to develop industry leading science and technology and promote these clinical improvements across our network of services and indeed the wider industry.

In 2016, the Group successfully submitted over 50 scientific papers and presentations both locally and internationally. A number of these research initiatives have already provided us with stepped improvements to our already leading treatment methods.

Monash IVF Group understands the importance of committing to ongoing scientific and clinical innovation, combined with the development of future leaders in the fields of reproductive medicine and women's imaging and diagnostics. Ultimately our aim is this commitment will benefit those pursuing their dream to create a family of their own.

On behalf of the Monash IVF Group Board, I commend the MREF and relay my thanks to our doctors, staff and collaborators who have contributed to this important body of work.

A word from the Chairman of the Monash IVF Research and Education Foundation

Professor Robert McLachlan AM | Chairman MREF

The Monash IVF Group's commitment to research and education has again been evident as it maintains its leadership position in assisted reproductive treatment.

As Chairman of MREF over the past eight years, I enjoy the strong and continuing support of the Monash IVF Managing Director and the Board of Directors. Our work also benefits from the fact that many members of MREF also hold appointments within Monash and Adelaide Universities resulting in outstandingly productive relationship with their research and teaching staff. Finally I acknowledge the generous untied research grants received from industry.

The MREF Advisory Board comprises clinical, embryological and medical imaging expertise and has worked with enthusiasm and creativity to develop programs that address our strategic goals. The outcomes of papers and presentations for 2016 and our future research directions are outlined in this report.

I express my gratitude to Professor Luk Rombauts, Director of Clinical Research, for his commitment and expertise in the conduct of our many clinical studies. We both recognise the invaluable work of our dedicated research team; Vivien MacLachlan (Data and Research Managers), Samantha Ter and Ann Wilson who diligently oversee the clinical studies and deals with the complex demands of the medical, nursing and scientific staff, and human ethics committees.

In 2016 our education program saw the continuation of the alliance between the Monash University EPRD and MREF. I would also like to thank all the Monash IVF Group clinical and scientific staff for their contributions to the educational programs we provide to undergraduate, postgraduate and overseas trainees.

Advisory Board

Monash IVF Group Research and Education Foundation

Professor Robert McLachlan AM
MBBS (Hons), PhD, FRACP

Director of Clinical Research, Hudson Institute of Medical Research; Adjunct Professor, Monash Department of Obstetrics and Gynaecology; Director, Andrology Australia; Monash IVF Consultant Andrologist

Graduating from Monash University in 1977 and completing advanced training in endocrinology in 1984, Professor Rob McLachlan undertook his PhD studies in reproductive physiology at Prince Henry's Institute and the Department of Anatomy, Monash University. He worked as a visiting scientist at the University of Washington, in Seattle, USA, working on the hormonal regulation of reproductive function. After returning to Australia in 1990, he has since attracted continuous funding as a Research Fellow of the NH&MRC. He has been the Consultant Andrologist to the Monash IVF program since 1991.

He is an Adjunct Professor in the Department of Obstetrics and Gynaecology at Monash University. As Director of Clinical Research at the Hudson Institute at Monash Medical Centre, he conducts NHMRC supported research involving basic and clinical research into male fertility regulation and the role of androgens, and is Deputy Director of Endocrinology, Monash Medical Centre. He has been Director of Andrology Australia, a Federal government initiative, based at Monash University since 2006, and is committed to research and community and professional education in male reproductive health.

Since 2006, he has made 62 invited presentations including 31 international presentations (keynotes and plenaries). He has published 249 original reports, reviews and chapters. He is Section Editor "Male Endocrinology" for www.ENDOTEXT.org; and is on several editorial boards, and is a consultant on male fertility regulation to the World Health Organisation. He is a Past President of the Fertility Society of Australia. In 2014 he received the Hoffenberg International Medal, Society for Endocrinology, UK, for outstanding contributions to the field and in 2016 was made a Member (AM) in the General Division of the Order of Australia in recognition of his work in male reproductive health and research.

Professor Luk Rombauts
PhD, MD, FRANZCOG, CREI

Group Medical Director, Monash IVF; Vice-President of the Fertility Society of Australia, Clinical Adjunct Professor, Department of Obstetrics and Gynaecology, Monash University; Head of Reproductive Medicine, Monash Health; IVF Specialist, Monash IVF

Trained in obstetrics and gynaecology at the University of Leuven, Belgium, in 1994, Prof Rombauts began his clinical and research work at Monash in 1994. After spending a further 2 years in the IVF unit at the Leuven Institute of Fertility and Embryology (Belgium), Prof. Rombauts returned to Melbourne in 1998 to obtain his Certificate of Reproductive Endocrinology and Infertility (CREI). He is now accredited by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists as a training supervisor and examiner for the CREI.

Prof. Rombauts has a strong track record in women's health, clinical and translational research in the field of reproductive medicine. He currently conducts NHMRC funded research into several aspects of female infertility, with a strong focus on the communication between the embryo and the endometrium. Professor Luk Rombauts has published a total of 115 articles, reviews and book chapters since 1990. He has a current h-index of 25 (Web of Knowledge 2016) and 1592 total citations. He has been invited to present lectures at numerous international meetings. He has helped develop clinical guidelines for the management of PCOS, endometriosis and OHSS. He is also an expert advisor for the Endometriosis Phenome and Biobanking Harmonisation Project sponsored by the World Endometriosis Research Foundation.

He is an Adjunct Clinical Professor in the Department of Obstetrics and Gynaecology at Monash University and the Head of Reproductive Medicine at Sothern Health. He is the Group Medical Director and Clinical Research Director of Monash IVF and a Research Fellow of the Hudson Institute for Medical Research. Prof. Rombauts was elected as Vice-President of the Fertility Society of Australia in 2015 and is a member of the IVF Directors Group Executive

Committee. He is a Board Member of the World Endometriosis Society in 2008. In 2011 he was appointed to the World Endometriosis Research Foundation Board of Trustees. He is also a member of the RANZCOG Grants and Scholarship Committee.

His clinical interests are advanced laparoscopic surgery for endometriosis, male and female reproductive microsurgery, and the management of male and female infertility.

Professor Beverley Vollenhoven
MBBS (Hons), PhD, FRANZCOG, CREI

Professor Vollenhoven graduated from Monash University in 1984 and completed her training in Obstetrics and Gynaecology in 1995. She has been a clinician at Monash IVF since 1996 and has a sub-specialty qualification in Reproductive Endocrinology and Infertility (CREI).

Her areas of clinical interest include infertility, polycystic ovarian syndrome, eating disorders, paediatric and adolescent gynaecology and menopause. She also has a clinical and research interest in the cause and treatment of uterine fibroids (leiomyomas); the management of infertility, particularly IVF, ovulation and ovulation disorders (such as PCOS), Turner's Syndrome and menopause.

She has more than 100 publications in both journals and books.

Professor Vollenhoven is the Head of Gynaecology at Monash Health and also of the Contraceptive Counselling Clinic and Menopause Clinic, Monash Medical Centre. She is a reproductive endocrinologist is the Long Term Care of Children with Cancer Clinic.

She is a Past Chairperson of the Victorian Regional Committee of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and is a member of the Examinations Committee and is currently an examiner for both the specialist and sub specialist exams. She was a member of the 8th Council of RANZCOG. She is a member of the Advisory Committee on Medicines as well as the Device Committee, both subcommittees of the TGA. Professor Vollenhoven was appointed Director of Teaching and Learning, MREF in June 2012.

Ms Jayne Mullen
BSc, MRM

Scientific Director, Monash IVF Victoria

Jayne Mullen completed her Bachelor of Science degree at the University of Western Australia (UWA) and her Masters in Reproductive Medicine at the University of New South Wales (UNSW).

Jayne joined Monash IVF in 2016 and is the current Scientific Director in Victoria. Jayne has over 20 years of experience in the ART industry and has worked in clinics in Australia and also spent many years practicing embryology in Europe. Jayne is a Senior Clinical Embryologist certified by the European Society of Human Reproduction and Embryology (ESHRE).She also lectures at the Masters of Clinical Embryology and Graduate Diploma of Reproductive Science courses at Monash University.

At Monash IVF, Jayne oversees operational performances of the Embryology and Genetics laboratories, including auditing and training, NATA and RTAC accreditation & compliance, quality management and implementation of innovative technologies. Jayne is dedicated to achieve optimal conditions in the laboratories to ensure the most advantageous results are achieved in maximising fertilisation rates and embryo development. Jayne monitors multiple key performance indicators in the laboratories to ensure the highest pregnancy successes for patients. Her main research interests are in improving ICSI and embryo biopsy techniques, eggs and embryo cryopreservation and optimal embryo selection.

Associate Professor Peter Benny MB ChB FRCOG FRANZCOG CREI

Medical Director Monash IVF and Next Generation Fertility

Assoc Prof Peter Benny is a fertility specialist. Pete is a sub specialist in Reproductive Endocrinology and Infertility. He studied medicine at the University of Otago and trained in Obstetrics and Gynaecology in Christchurch NZ and Leicester UK. Pete has a wide experience in Obstetrics and Gynaecology and has been involved in infertility management and IVF for more than 25 years. Until 2010 he was Medical Director of Repromed Christchurch, before shifting to Sydney. In the past he has had leading roles in The Fertility Society of Australia and the Reproductive Technologies Accreditation Committee.

He is currently the chairman of the examination committee for the CREI of RANZCOG and is Medical Director for Monash IVF New South Wales and Monash IVF Parramatta. Pete's interests in fertility and reproductive medicine are broad but are particularly in education and training, with extensive experience in; surgical conditions associated with infertility management, ovarian responsiveness and reserve, and factors of nutrition, aging and environment that impact on male and female fertility.

Clinical Associate Professor Fabricio Costa MD, PhD, FRANZCOG, DDU, COGU, DipFM

Obstetrician Sonologist, Monash Ultrasound for Women

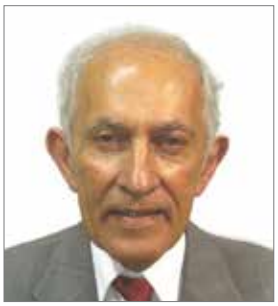
A/Prof Fabricio Costa graduated in Medicine in 1995. He was awarded a PhD in 2001 from the University of Sao Paulo, Brazil, for Doppler studies in the prediction of pre-eclampsia. He received board certification in obstetrics and gynaecology with subspecialty training in obstetric and gynaecological ultrasound. In 2005, Dr Costa became an Associate Professor in obstetrics and gynaecology and served as a board member in a variety of Brazilian Medical Associations. In 2009, Dr Costa moved to Australia as a Clinical/Research Postdoctoral Fellow in fetal medicine and ultrasound in obstetrics and gynaecology at the Royal Women's Hospital in Melbourne. Dr Costa was awarded Fellowship of The Royal Australian and New Zealand College of Obstetricians and Gynaecologists in 2011, and Diploma of Diagnostic Ultrasound (DDU) and Certification in Obstetric and Gynaecological Ultrasound (COGU) in 2012.

In 2014 Dr Costa was promoted to Deputy Director, Ultrasound Services, Royal Women's Hospital and Clinical Associate Professor at the Department of Obstetrics and Gynaecology, University of Melbourne. In early 2016, A/Prof Fabricio Costa moved to Perinatal Services, Monash Medical Centre in order to set up a clinical/academic first trimester screening program at Monash Health and he also joined the Monash University Department of Obstetrics and Gynaecology as an Adjunct Clinical Associate Professor.

He has over 70 peer-reviewed publications and he is a frequent speaker in national and International conferences related with ultrasound in obstetrics and gynaecology and maternal-fetal medicine. Currently he is a member of the Australasian Society for Ultrasound in Medicine (ASUM) Council and an Ambassador of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) to Brazil and Australasia. His clinical and research interests focus on the use of ultrasound in maternal-fetal medicine, especially pre-eclampsia, fetal growth restriction and preterm labour. In addition, he has special interest in first trimester screening, including non-invasive prenatal testing (NIPT).

In 2014 Dr Costa was promoted to Deputy Director, Ultrasound Services, Royal Women's Hospital and Clinical Associate Professor at the Department of Obstetrics and Gynaecology, University of Melbourne. In February 2016 Dr Costa was appointed Medical Director of Monash Ultrasound for Women, a leading private practice in Melbourne. He was also appointed Visiting Medical Officer at Monash Medical Centre (the largest maternity service in Victoria) and Clinical Associate Professor at the Department of Obstetrics and Gynaecology, Monash University. Currently he is a member of the Australasian Society for Ultrasound in Medicine (ASUM) Council and an Ambassador of the International

Society of Ultrasound in Obstetrics and Gynecology (ISUOG) to Brazil and Australia. A/Prof Costa's clinical and research interests focus on the use of ultrasound in maternal-fetal medicine, especially pre-eclampsia, fetal growth restriction and preterm labour. In addition, he has special interest in first trimester screening, including non-invasive prenatal testing (NIPT).



Professor David de Kretser AC
MBBS, MD, FRACP, FAA, FTSE, FAHMS, Hon LLD (Monash), Hon LLD (Melbourne), FRANZCoG (Hon), FRCOG (Hon)

Sir John Monash Distinguished Professor, Hudson Institute Medical Research, and Department of Anatomy and Developmental Biology, Monash University

Professor de Kretser is a reproductive endocrinologist whose appointments at Monash have included Professor of Anatomy, the founding Director of the Monash Institute of Medical Research (now the Hudson Institute) and the Associate Dean for Biotechnology Development. He is a Fellow of the Australian Academy of Science, a Fellow of the Australian Academy of Technological Sciences and Engineering, a Fellow of the Australian Academy of Health and Medical Sciences and a Fellow of the Royal Australasian College of Physicians. Following a term as the 28th Governor of Victoria from 2006 to 2011 he has returned to pursue research as a Sir John Monash Distinguished Professor.

His reproductive research program encompasses the causes of male infertility, control systems involved in ovulatory mechanisms and exploring novel causes of developmental abnormalities of the genitalia. He established that activin A, as well as stimulating FSH secretion, is a proinflammatory cytokine that is involved in the initiation of the inflammatory responses regardless of the inflammatory stimulus. Following the isolation of follistatin, together with his colleagues, he established that it modulates the inflammatory response by binding activin A and decreasing its bioactivity. This data has led to a program of research designed to develop treatments for inflammatory diseases such as cystic fibrosis and acute lung injury. These discoveries led to the formation of Paranta Biosciences. a company with the goal of the commercial development of follistatin, as an anti-inflammatory and anti-fibrotic regulator. He also has an interest in community and professional education in male reproductive health.

Professor Michelle Lane BSc, PhD

Regional Manager, Monash IVF Group

Prof Michelle Lane is currently a Senior Lecturer with the Research Centre for Reproductive Health.

She received her PhD 1996 and then spent 2 years at the University of Wisconsin as a post-doctoral fellow before moving to take up a Senior Scientist position at the Colorado Center for Reproductive Medicine. She has combined her research appointments with clinical embryology since 1992 when she moved to a scientific advisor role to 2 clinics in the USA and then Scientific Director. At the end of 2003, Dr. Lane returned to Australia at the University of Adelaide to establish a clinical orientated research program in the area of mammalian embryology and oocyte biology. In 2004 she was awarded a 'Tall Poppy' award for recognition of excellence for young biomedical researchers in South Australia. In 2005, she began as a NHMRC RD Wright Fellow.

Dr. Lane has published extensively in the area of preimplantation embryology and has co-authored 51 premier peer-reviewed journals (including Nature Biotechnology, Journal of Biological Chemistry, Developmental Biology and Biology of Reproduction, the highest impact factor reproduction journal), 11 review articles, edited 2 books and written 17 book chapters. Her intellectual input into this published research is demonstrated by the number of first and last author publications attributed to her (53 publications). Dr. Lane is an innovative researcher with extensive experience in intellectual property protection and commercialisation as evidenced by being an inventor on several different patent applications Dr. Lane has established herself as a highly motivated researcher with a growing international reputation.

Ms Kate Watson
BBiotech, MBE

Embryologist, Monash IVF Group

Kate completed her Bachelor of Biotechnology at The University of Newcastle. Kate had the opportunity to undertake a research project under the guidance of Laureate Professor John Aitken and Associate Professor Brett Nixon during the final year of her degree. This instilled a passion for reproductive science and research. After graduating Kate began working as an embryologist and completed a Masters in Bioethics from Monash University. This gave her an insight into the complex ethical issues encountered in a clinical IVF setting. Kate currently works at Monash IVF Gold Coast as an embryologist. As an integral member of the experienced team Kate coordinates the PGS program at the Gold Coast ensuring the suite of genetic screening/testing is available for our Queensland patients. Kate's areas of interest include blastocyst culture and embryo biopsy, pre-implantation genetic screening, improving patient outcomes through improved culture conditions and exploring the ethical implications of IVF technology.

Dr Deirdre Zander-Fox
BSc (Hons), PhD, Dip Mgt

Regional Scientific Director for the Monash IVF Group (Repromed, MyIVF, MonashIVF QLD, KL Fertility)

Deirdre completed her PhD studies in 2009 through The University of Adelaide's School of Paediatrics and Reproductive Health in which she undertook novel research into the impact of in-vitro stress on preimplantation embryo development, viability and metabolism. She has been at Repromed since 2004 and is currently Regional Scientific Director for the Monash IVF Group which includes the clinics: Repromed (SA and NT), MyIVF and Monash IVF QLD and KL fertility. Deirdre is responsible for Embryology, Genetics, Andrology and Endocrine services within these clinics as well as operational management, QC/QA and new technology implementation. In addition Deirdre is also a Visiting Research Fellow at The University of Adelaide's School of Paediatrics and Reproductive Health where she supervises Honours and PhD student research, is a research collaborator at University of SA where she supervises a PhD student, is a lecturer for Human Reproductive Health III and Comparative Reproductive Biology of Mammals at the University of Adelaide, and in 2014 was named one of SA's young tall poppies.

Deirdre has authored 25 peer reviewed journal articles, reviews and book chapters with her research focusing on improving laboratory technology that will directly benefit infertile patients including cryopreservation, culture media design and metabolic screening of embryo culture media. Her basic research interests focus on the impact of the environment during peri and pre implantation development on programming fetal growth and offspring health for which she has received NHMRC funding in collaboration with Professor Michelle Lane.

A word from the Director of Education

Professor Beverley Vollenhoven

Our partnership with Monash University's Education Program in Reproduction and Development (EPRD) continues to develop.

Clinicians and embryologists provide teaching for both the Diploma and Masters courses and in 2016 there was a further collaboration in teaching with visitors from Diponegoro University, Indonesia and Gadjah Mada University, Indonesia who attended the short course in Basic Assisted Reproductive Technology & Infertility Management. The Monash Observership Program also continued in 2016. We provided tailored training to clinical specialists, Dr Yassin Mohammad from Indonesia, Dr Poornima Durga and Dr Mathew Papachen from India.

A word from the Director of Clinical Research

Professor Luk Rombauts

It is very pleasing to see how productive the Monash IVF Group Research and Education Foundation has been in 2016.

Three NHMRC funds have been granted in the year of 2016. Special congratulations to Rob McLachlan, the chairman of MREF for obtaining two NHMRC grants. Some exciting new research studies have also commenced, including studies of embryo mosaicism and investigation of adenomyosis using 3D ultrasound scans. In addition, I would like to thank the research team; Caroline Motteram, Ann Wilson and Samantha Ter, for coordinating the ethics and recruitment for the ever growing number of projects that we now have in our research portfolio. My gratitude also goes out to Vivien MacLachlan. She is an irreplaceable member of the research team with her invaluable data management skills and a perfect corporate memory.

Research Highlights 2016

"The MREF supports research that takes basic scientific understanding into the clinical setting so as to provide new safe and effective treatments for our patients."

MREF has a diverse research portfolio covering male and female reproductive biology, genetics and molecular science, clinical practice, reproductive tract imaging, psychosocial research and maternal and fetal wellbeing.
In 2016 our research program saw the continuation of our successful collaborations with the Hudson Institute, Monash University, Queensland University of Technology, The University of Adelaide and The Murdoch Children's Research Institute. These initiatives continue to make a valuable contribution to improving the understanding of embryo-endometrial interactions, early embryonic development and optimal treatments for couples and their offspring.
Highlights for 2016 included:

• The MREF continues to engage in clinical trials which focus on evaluating and implementing the latest scientific technologies and therapeutic approaches. Accordingly MREF was excited to have our new Scientific Director Victoria, Jayne Mullen, join the board and take charge of the research direction in embryology and the emerging genetic technologies.

• In 2016 Dr Shavi Fernando (Monash Health) completed his PhD work supported by the Ella Macknight Memorial Scholarship by the RANZCOG Foundation. This study was the first double blinded placebo-controlled dose-response trial assessing the effect of melatonin on IVF outcomes on the clinical efficacy of melatonin supplementation in IVF and the results will be published shortly

• MREF Senior staff continued to have a high profile at major meetings. At the 6th Congress of the Asia Pacific Initiative on Reproduction (ASPIRE 2016) in Jakarta, Prof Luk Rombauts made an invited presentation on 'The endometrium in IVF: Endometrial markers of implantation' and Prof Robert McLachlan presented on the "Investigation of the male prior to IVF and outcomes for the child". In May, Dr Fabricio Costa presented at the Second International Congress on Maternal Hemodynamics in Rome, Italy on the "Interlobar renal vein Doppler as a first trimester predictor of pre-eclampsia' and was award the "Best oral presentation".

Finally Assoc Prof Kelton Tremellen presented on 'You are what you eat; mechanisms by which the gut can effect reproduction.' The 10th Biennial Conference of the Association of Clinical Embryologists; in Newcastle, UK.

• At national meetings, Monash IVF Group research activities were presented at the Fertility Society of Australia meeting on topics including the effect of adjuvant therapies on pregnancy rates in IVF, preimplantation genetic diagnosis and the use of external quality assurance programme in ART. At the Scientists in Reproductive Biology Meeting (SIRT) on behalf of the Repromed team, Leanne Pacella-Ince's talk on detection of Robertsonian translocations using Next Generation Sequencing won the Established Scientist Award while Helana Shehadeh's paper on the impact of antioxidant supplementation in overweight and obese men on sperm quality, sperm function, embryo development, and pregnancy rates was granted the 'Young Scientist Award. Finally at the Royal Australian and New Zealand College of Obstetricians and Gynaecologists meeting, Prof Kelton Tremellen presented on differences in fetal growth and pregnancy outcomes between fresh and frozen embryo transfer and progesterone supplementation in frozen embryo transfer with hormone replacement therapy.

• 2016 was an excellent year for our male infertility team with the awarding of two extremely competitive NHMRC project grants with investigators at the Hudson Institute on the genetic causes of male infertility, with additional investigators from Monash University and in the Netherlands and USA.

• To benchmark our management of male infertility, our embryologist Dr Sandra Holden undertook an exchange scholarship to attend ART Programmes at Cornell and Chicago and to attend the ASRM.

• Over 30 papers were published across the group in 2016 and we expect that this strong publication activity will continue.

Monash IVF

COMPLETED RESEARCH

Melatonin and infertility: can we improve outcomes of assisted reproductive technology - a randomised placebo controlled trial

Dr Shavi Fernando[1], Prof Luk Rombauts[1,2], Prof Beverley Vollenhoven [1,2], Caroline Motteram[2], Dr Tiki Osianlis[1], Prof Euan Wallace[1].

[1]Monash Dept Obstetrics and Gynaecology, Clayton; [2]Monash IVF, Clayton.

During ART, eggs and embryos may interact negatively with oxygen molecules in a process called 'oxidative stress'. In recent years, interest has gathered regarding the role of oxidative stress on the quality of stored eggs and embryos, potentially reducing success rates and live birth rates following ART. It is proposed that melatonin, a potent antioxidant, may help reduce the effect of oxidative stress on eggs and embryos. The aim of this randomised placebo controlled trial is to determine whether melatonin supplementation can increase serum and follicular fluid levels of melatonin, reduce oxidative stress markers and improve ART outcomes. Data will be gathered looking at oocyte number and quality, embryo number and quality, ultrasound Doppler flow to the ovaries and uterus, sleep patterns, pregnancy rates and live birth rates. Through this well-designed trial we hope to determine whether melatonin is a useful additional therapy in ART to further inform both clinicians and the general public about how we might further improve outcomes for infertile couples.

The proliferative phase underpins endometrial receptivity failure in female infertility

Harriet Fitzgerald[1,2], Prof Lois Salamonsen[1,2], Prof Luk Rombauts[1,2,3], Prof Beverly Vollenhoven[1,2,3], Dr Tracey Edgell[1,4].

[1]Centre for Reproductive Health, Hudson Institute of Medical Research, Clayton; [2]Department of Obstetrics and Gynaecology, Monash University; [3]Monash IVF, Clayton; [4]Monash University, Clayton.

The endometrium is the lining of the uterus, into which an embryo implants to establish pregnancy. The human endometrium is uniquely renewed each month during a menstrual cycle, which comprises three main phases, beginning with the shedding of the functional layer of the endometrium and its re-epithelialisation (the menstrual phase), followed by the regrowth and proliferation of all endometrial cell types and development of the glands. Endometrial gland development occurs during the proliferative phase of a woman's menstrual cycle, laying the foundation for the subsequent receptive, secretory phase when pregnancy is established.
Idiopathic infertility has been rarely investigated with respect to the proliferative phase endometrium. We investigated whether gland development and/or altered secretion of cytokines during the proliferative phase is associated with infertility.
We assessed the numbers of glands in endometrial tissue and applied cytokine screening and proteomic techniques to identify dysregulation within uterine lavage, from the proliferative phase of fertile and infertile women. This study indicates for the first time, that the proliferative phase uterine microenvironment is altered in younger infertile women compared to fertile women.

Intrauterine human chorionic gonadotropin (hCG) infusion prior to embryo transfer (ET) may be detrimental to pregnancy rate

Michelle Volovsky[1], A/Prof Martin Healey[2], Vivien MacLachlan[3], Prof Beverly Vollenhoven[4].

[1]Monash University, Clayton; [2]University of Melbourne, Malvern East; [3]Monash IVF, Richmond; [4]Obstetrics and Gynaecology, Monash University, Clayton.

The process of embryo implantation is influenced by both embryonic and endometrial factors. The receptivity of the endometrium is vital to the process and hence much attention has been given to enhancing the intrauterine environment. A hormone thought to have beneficial effects on this environment is hCG. It has been postulated that an intrauterine hCG infusion prior to ET could potentially increase implantation rates. However, up to this point, evidence on the matter is conflicting. Our aim was to investigate whether intrauterine hCG at the time of ET improves pregnancy rate.

ONGOING RESEARCH

Fertility Understanding through Registry and Evaluation (FUTuRE Fertility)

Dr Antoinette Anazodo[1], Professor Elizabeth Sullivan[2], Prof Robert McLachlan[3,4], Prof Luk Rombauts[4,5].

[1]Sydney Children Hospital, Randick; [2]Women's and Children's Health, Randick; [3]Hudson Institute of Medical Research, Clayton; [4]Monash IVF, Clayton; [5]Monash Dept Obstetrics and Gynaecology, Clayton.

This project will establish the first web-based, Australasian Oncofertility Registry (AOFR) collecting data from cancer and fertility centres. The study focuses on children and young adults who have been diagnosed with cancer and may receive cancer treatment. The project will monitor uptake and use of fertility preservation (FP) as well as future use and complications of assisted reproductive therapies (ART).

Data from the registry and Medicare patient information will also be used to perform a cost modelling health economics study. This database will serve as a platform for research studies that will help us answer some of the questions concerning the fertility in cancer patients, so we can improve the fertility outcomes for cancer patients, i.e. their ability to have their own biological children in future. The outcomes from this study will also assist clinicians with provision of accurate risk projections for patient's future infertility and assist clinicians in making recommendations for FP/ART.

Role of endometrial stem/progenitor cells in the endometrial injury effect on ART outcomes: the fourth hypothesis

A/Prof Caroline Gargett[1], Germana Ryan[1], Prof Luk Rombauts[2,3], Dr Gareth Weston[2,3].

[1]Hudson Institute of Medical Research, Clayton; [2]Monash IVF, Clayton; [3]Monash Dept Obstetrics and Gynaecology, Clayton.

Recent studies show that biopsy-induced endometrial injury in the cycle prior to embryo transfer (ET) doubles live birth rates from IVF procedures. A Cochrane Systematic Review confirmed the safety and effectiveness of endometrial biopsy for improving ART outcomes. We propose that endometrial injury activates endometrial stem/progenitor cells, improving endometrial quality and promoting embryo implantation. This observational study aims to quantify our markers of endometrial stem/progenitor cells (W5C5 and CDH2) in endometrial biopsies obtained from infertile women in the cycle prior to ET, and determine their relationship with clinical pregnancy/live birth rates and endometrial thickness. This study will suggest a novel mechanism to explain increased pregnancy rates observed with endometrial injury/"scratching" and provide the first data linking this observation with endometrial stem/progenitor cells in tissue. It will increase our understanding of how a thick receptive endometrium can be generated for IVF-ET protocols to significantly improve ART outcomes.

Monash IVF (continued)

Developing a non-invasive screening tool for Aneuploidy

Dr Eva Dimitriadis[1], Prof Luk Rombauts[2,3], Dr Tiki Osianlis[3].

[1]Hudson Institute of Medical Research, Clayton; [2]Monash IVF, Clayton; [3]Monash Dept Obstetrics and Gynaecology, Clayton.

Human oocytes display a high degree of aneuploidy and the incidence of these chromosomal abnormalities increases with maternal age. Increasingly, women of advanced age are seeking IVF. However, their likelihood of success is low due to the low number of euploid oocytes available. At present the only techniques available to assess the chromosomal state of an embryo are costly and invasive involving the removal of cells from pre-implantation stage embryos. A non-invasive test for embryo aneuploidy would be a major advance and constitute a significant benefit for patients undergoing IVF. Recently studies have shown that microRNA (miR) expression patterns differs in blastocyst trophectoderm tissue depending on their ploidity. Our pilot data showed that embryos secrete miRs in the culture media suggesting that miRNAs present in the culture media may present an avenue for the non-invasive identification of euploid embryos. Recent evidence has also suggested that time-lapse microscopy of IVF embryos during development is useful in identifying atypical development. The aim of this study is to develop a non-invasive test of aneuploidy. We will combine analysis of miRNAs secreted by embryos in culture media, time-lapse imagery of embryos during development and 24 chromosome screening. To confirm embryo ploidy, 24 chromosome screening will be correlated with the non-invasive tests.

Endometrial thickness and its association with uterine hyper-peristalsis in IVF

Dr Michelle Dunn[1], Prof Luk Rombauts[1,2], Dr Shavi Fernando[1], Samantha Ter[2].

[1]Monash Dept Obstetrics and Gynaecology, Clayton; [2]Monash IVF, Clayton.

This cohort study is investigating the subtle muscle contractions of the uterus known as “uterine peristalsis” during the time of implantation of an embryo into the uterus. It is thought that these contractions may be more prominent in women with a thicker endometrium. Although we don’t know for sure, these contractions may have the potential to shift the embryos into a different spot than where it was deposited. This study proposes that the thickness of the endometrial lining is related to these contractions; i.e. the thicker the endometrial lining the higher the frequency of the contractions. If a relationship between the thickness of the endometrium is linked to the uterine contractions it could potentially explain why embryos sometimes implant low in the uterine cavity or in rare circumstances end up implanting in the fallopian tube as an ectopic pregnancy. Additionally, this may lead to future studies looking at screening for and potentially treating higher risk women with medications to decrease uterine muscle activity at the time of transfer.

The effects of unrecognised Chlamydial infection on sperm production in human infertility

A/Prof Ken Beagley[1], Dr Danica Hickey[1], Emily Bryan[1], Prof Eileen MacLaughlin2, Prof Rob McLachlan[3], Prof Luk Rombauts[3,4], Samantha Ter[3], Dr Darren Katz[5].

[1]Queensland University of Technology, Brisbane; [2]University of Newcastle, Callaghan; [3]Monash IVF, Clayton; [4]Monash Dept Obstetrics and Gynaecology, Clayton; [5]The Centre for Specialist Men’s Health and Fertility, Melbourne.

Chlamydial infections are very common in our community with about 25% of people aged 25-35 yrs having past or current infections. Many people have no symptoms and therefore don’t receive treatment and as a result, chronic infections may occur that damages reproductive tissues in females and potentially in males. We now believe that Chlamydial infection of the testis can damage sperm production leading to infertility.

The purpose of this research is to investigate whether male infertility can be caused by the sexually transmitted infection, Chlamydia. Testicular tissue obtained after testicular biopsy will be used to find out the effects of possible unrecognized infection on sperm development, and the ways this damage occurs. We hope to develop methods for early diagnosis of infections.

Endometrial receptivity: validating potential biomarkers in the uterine fluid and investigating fundamental biology on the uterine surface

A/Prof Guiying Nie[1], Prof Luk Rombauts[2,3], Prof Beverley Vollenhoven[2,3].

[1]Hudson Institute of Medical Research, Clayton; [2]Monash IVF, Clayton; [3]Monash Dept Obstetrics and Gynaecology, Clayton.

Embryo culture/selection/transfer techniques have advanced greatly, yet implantation failure still poses a crucial limiting factor. It is believed that the hurdle may lay in the "soil for the seeds", the endometrium. Currently no biochemical tests are available for endometrial receptivity, and in ART cycles embryos are transferred without knowing the status of the endometrium. Development of diagnostics for endometrial receptivity is critical to improve ART outcomes. Our studies have identified a number of biomarkers for receptivity. In particular, 3 proteins warrant further investigation: PC6, a critical regulator for receptivity; α-DG-N, a protein released from the uterine surface into the cavity at receptivity; and PDGFAA, a growth factor newly identified as a potential receptivity biomarker. We have established specific assays for PC6 and α-DG-N, whereas a PDGFAA ELISA is already commercially available. We aim to validate these 3 candidates in large cohorts of uterine fluids and to uncover the fundamental aspects of endometrial epithelial receptivity.

Human trophectoderm-endometrial interactions: validating targets to facilitate implantation during IVF

A/Prof Eva Dimitriadis[1], Prof Luk Rombauts[2,3], Dr Tiki Osianlis[3].

[1]Hudson Institute of Medical Research, Clayton; [2]Monash IVF, Clayton; [3]Monash Dept Obstetrics and Gynaecology, Clayton.

During embryo implantation blastocysts appose and firmly adhere to a receptive endometrium initiating implantation: adhesion leads to implantation failure/infertility. There is very little known of human blastocyst-endometrial interactions. Identifying the critical regulators at the time of implantation may identify targets to facilitate implantation during IVF. To address this gap in knowledge we developed a unique model where we collected blastocyst conditioned media (BCM) from clinical leftovers from blastocysts that were transferred during IVF and either successfully implanted or did not implant. We used this media to treat primary human endometrial epithelial cells in vitro and demonstrated that blastocysts release small non-coding RNAs, microRNAs (miRs). We propose that blastocysts release miRs in vivo which regulate blastocyst-endometrial interactions during implantation. Blastocysts that are destined for implantation failure will release miR abnormally and will alter implantation and result in infertility. In the present proposal we aim to confirm our findings and determine the effect of the identified differentially altered miRs on trophectoderm-endometrial adhesion in vitro, the initiating event of implantation. This will provide functional in vitro evidence for the first time for whether targeting these interactions during embryo transfer may facilitate implantation.

Monash IVF (continued)

Studies on the genetic basis of male and idiopathic infertility, and the trans-generational health of children conceived through ART

A/Prof Moira O'Bryan[1], Dr Liza O'Donnell[2,3], Prof Robert McLachlan[3,4], Dr Duangporn Jamsai[1], Prof Andrew Sinclair[5], Dr Alicia Oshlack[5].

[1]Dept. Anatomy and Developmental Biology, Monash University; [2]Monash Institute of Medical Research; [3]Hudson Institute of Medical Research, Clayton; [4]Monash IVF, Clayton; [5]The Murdoch Childrens Research Institute.

Infertility affects 1 in 20 Australian men and leads to approximately half of all ART treatments. Male infertility is often due to the failure to produce adequate numbers of motile sperm capable of fertilisation. Genetic factors are suspected to be causal in many cases. Understanding such genetic factors may result in new diagnostic tests and ultimately specific treatments. Such research may also address uncertainties around the possible transmission of infertility to ART conceived offspring. Based on our extensive mouse gene discovery program, we have identified many genes with essential roles in male mouse fertility. As an extension of this work, and using a bioinformatics approach, we are systematically screening human male samples for mutations likely to cause infertility. Recent findings include an evolutionarily conserved association between Sertoli cell only syndrome in mice and humans, and mutations in the ETV5 gene.

Podocalyxin may represent a major barrier for endometrial receptivity

A/Prof Guiying Nie[1], Dr Sarah Paule[1], Prof Luk Rombauts[2,3], Prof Beverley Vollenhoven[2,3].

[1]Hudson Institute of Medical Research, Clayton; [2]Monash IVF, Clayton; [3]Monash Dept Obstetrics and Gynaecology, Clayton.

ART has progressed into an important medical intervention to overcome infertility. However, despite significant advancements in embryo culture, selection and transfer techniques, implantation failure still poses a crucial limiting factor. It is believed that the problem is the "soil for the seeds", the endometrium. For implantation to occur, the endometrium must differentiate into a receptive state. As the embryo first contacts the surface of the endometrial epithelium, this surface must become adhesive for embryo attachment. Although it is known that the endometrial epithelium remodels structurally and functionally to gain receptivity, the exact molecular changes are not well understood. Our previous proteomics studies have identified a number of molecules that are drastically altered in the endometrial epithelium for receptivity; one of which is an anti-adhesive molecule called podocalyxin (PODXL). Our preliminary data strongly suggest that PODXL is an anti-adhesive molecule presented on the apical surface of endometrial epithelium and that endometrial receptivity is accompanied by PODXL removal. We aim to show that PODXL is an important barrier of endometrial receptivity and failure of PODXL removal is associated with endometrial infertility.

STREAM: Effect of ovarian stimulation on oocyte quality and embryonic aneyploidy: a prospective, randomised controlled trial

Prof Rob Norman[1], A/Prof Louise Hull[1], Dr Tristan Hardy[2], Prof Luk Rombauts[3], Prof William Ledger[2,4], Prof Michael Chapman[4], A/Prof Anusch Yazdani[5], Dr Alex Polyakov[6], Prof Kelton Tremellen[7], Prof Roger Hart[8].

[1]Fertility SA, Adelaide; [2]University of New South Wales, Kensington; [3]Monash IVF, Clayton; [4]IVF Australia, Bondi Junction; [5]Queensland Fertility Group, Spring Hill; [6]Melbourne IVF, East Melbourne; [7]Repromed, Dulwich; [8]Fertility Specialists of Western Australia, Claremont.

Oocyte derived aneuploidy is the leading cause of IVF failure, early pregnancy loss, and the age-related decline in female fertility. Selection of the dominant follicle during unstimulated cycles is thought to act as a quality control mechanism by selecting the most competent oocyte in a cohort of available follicles. By contrast, controlled ovarian hyperstimulation is used to maximise the number of oocytes collected during IVF cycles and has been implicated as a cause of aneuploidy at the cleavage stage due to recruitment of poor quality oocytes.

There have been no studies comparing aneuploidy at D5 or D6 of development using comprehensive chromosome screening techniques, now widely considered the gold standard in preimplantation genetic screening. As such, there continues to be variation in clinical practice regarding ovarian stimulation. Some clinicians aim to retrieve fewer oocytes (e.g. <14) and use lower doses while other clinicians aim to retrieve more oocytes (~20+) and use higher doses of gonadotropins routinely, with the strategy of vitrifying all embryos becoming more common. STREAM is a prospective, multicentre, randomised controlled trial to compare two different stimulation regimens with universal preimplantation genetic screening using next generation sequencing (NGS). In addition, we will use newer techniques such as mtDNA copy number quantification to provide additional information regarding oocyte quality allowing a more comprehensive assessment of the impact of ovarian stimulation on oocyte quality.

Clinical significance of undiagnosed mosaicism in IVF embryos

Dr Elissa Willats, Claire Lillee, Dr Jane Lin, Dr Lee-Yean Low, Jayne Mullen, Prof Luk Rombauts.

Monash IVF, Clayton

Preimplantation Genetic Screening (PGS) is used to diagnose chromosome copy number in IVF embryos prior to implantation. Embryos which are diagnosed as chromosomally normal (ie: euploid; potential to result in a healthy ongoing pregnancy) are selected for transfer in a frozen embryo transfer cycle. Embryos which are diagnosed as chromosomally abnormal (ie: aneuploid; expected to result in implantation failure, miscarriage or abnormalities at birth) are not considered suitable for transfer. PGS should result in the transfer of embryo/s that have a higher chance of implantation and development to term, and should lead to a concomitant decrease in the rate of spontaneous abortions and abnormalities at birth.

PGS technologies have advanced rapidly over the past few years. PGS is currently performed using Next Generation Sequencing (NGS), which is superior at detecting mosaicism in embryo biopsy samples compared with previous PGS techniques such as aCGH (Munne et al 2016, Spinella et al, 2016). Approximately 25% of IVF embryos are diagnosed as mosaic (ie: containing both normal and abnormal cells) following PGS using NGS. These embryos are currently considered abnormal and not suitable for transfer. The project will add to the existing knowledge in this under-researched field and contribute directly to improve our knowledge of mosaicim.

Monash IVF (continued)

Contributions to Scientific Literature

The following compiles a portfolio of contributions to the scientific literature by Monash IVF staff and key collaborators for 2016. The list represents our commitment to broad range of research interests spanning reproductive biology, genetic and molecular, andrology, clinical and psychological based research.

Peer Reviewed Journal Articles/Publications

1. **Anazodo AC, Gerstl B, Stern CJ, McLachlan RI, Agresta F, Jayasinghe Y, et al.** Utilizing the Experience of Consumers in Consultation to Develop the Australasian Oncofertility Consortium Charter. J Adolesc Young Adult Oncol. 2016 Mar 16.

2. **Anazodo AC, Stern CJ, McLachlan RI, Gerstl B, Agresta F, Cohn RJ, et al.** A Study Protocol for the Australasian Oncofertility Registry: Monitoring Referral Patterns and the Uptake, Quality, and Complications of Fertility Preservation Strategies in Australia and New Zealand. J Adolesc Young Adult Oncol. 2016 Mar 16.

3. **Cuman C, Van Sinderen M, Gantier MP, Rainczuk K, Rombauts L, Osianlis T, et al.** Human Blastocyst secreted microRNA regulate endometrial epithelial cell adhesion. EBioMed. 2015 Sep; 2(10): 1528-1535. Not included in 2015 MREF Annual report

4. **Fitzgerald HC, Salamonsen LA, Rombauts LJR, Vollenhoven BJ, Edgell TA.** The proliferative phase underpins endometrial development: Altered cytokine profiles in uterine lavage fluid of women with idiopathic infertility. Cytokine. 2016 Aug; 88: 12-19.

5. **Heng S, Vollenhoven B, Rombauts LJ, Nie G.** A High-Throughput Assay for the Detection of alpha-Dystroglycan N-Terminus in Human Uterine Fluid to Determine Uterine Receptivity. J Biomol Screen. 2016 Apr; 21(4):408-13.

6. **Humaidan P, Nelson SM, Devroey P, Coddington CC, Schwartz LB, Gordon K, et al.** Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. Hum Reprod. 2016 Jun 23.

7. **Hunt SP, Talmor A, Vollenhoven B.** Management of non-tubal ectopic pregnancies at a large tertiary hospital. Reprod Biomed Online. 2016 Apr 19.

8. **Menakaya UA, Rombauts L, Johnson NP.** Diagnostic laparoscopy in pre-surgical planning for higher stage endometriosis: Is it still relevant? Aust NZ J Obstet Gynaecol. 2016 Oct; 56(5): 518-822.

9. **Rombauts L, McMaster R, Motteram C, Fernando S.** Reply: Every cycle counts. Hum Reprod. 2016 Apr; 31(4):915-916.

10. **Shields R, Vollenhoven B, Ahuja K, Talmor A.** Ovarian hyperstimulation syndrome: A case control study investigating risk factors. Aust NZ J Obstet Gynaecol. 2016 Dec; 56(6): 624-627.

11. **Menon S, Scott HS, Logan B, Hocking JS, Timms P, Rombauts L, et al.** Development and evaluation of a multi-antigen peptide ELISA for the diagnosis of Chlamydia trachomatis-related infertility in women. Microbiol. 2016 Jul; 65 (9): 915-922.

12. **Simmonds MJ, Milne N, Ong K, Brotherton E, McNamee AP, Horobin J et al.** Physical properties of blood are altered in young and lean women with Polycystic ovary syndrome. PLoS ONE. 2016 Nov 30.

13. **Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B.** Uterine fibroids. Nat Rev Dis Primers. 2016 Jun; 23(2).

Presentations - National Conferences and Meetings

1. **Basnayake S, Volovsky M, MacLachlan V, Vollenhoven B, Healy M.** Dose-response of progesterone supplementation in frozen embryo transfer with hormone replacement therapy. Annual Meeting of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists; 2016, Oct 16 – 19; Perth, Australia

2. **Beyer C, Sugiana C, Osborne E.** Natural selection between day 3 and day 5/6 PGS embryos in translocation carrier couples. Annual Scientific Meeting of the Fertility Society of Australia; 2016, Sept 4 - 7; Perth, Australia.

3. **Beyer C, Osborne E.** Sixteen years of clinical PGS/PGS experience. Annual Scientific Meeting of the Fertility Society of Australia; 2016, Sept 4 - 7; Perth, Australia.

4. **Mackenzie J, Stanger J, Bakos HW.** Demonstration of nursing staff competency in follicle diameter assessment using an external quality assurance programme. Annual Scientific Meeting of the Fertility Society of Australia; 2016, Sept 4 - 7; Perth, Australia.

5. **Shirlow R, Healey M, Volovsky M, MacLachlan V, Vollenhoven B.** The Effect of Adjuvant Therapies on Pregnancy Rates in IVF. Annual Scientific Meeting of the Fertility Society of Australia; 2016, Sept 4 – 7: Perth, Australia

Presentations - International Conferences and Meetings

1. **Farquhar CM, Gillet W, Rombauts L, Macaldowie A, Chambers G.** Does rationing fertility treatment lead to better success rates? A population-based comparative analysis of Australian and New Zealand assisted reproductive technology cycle. European Society of Human Reproduction and Embryology 32nd Annual Meeting; 2016, July 3 – 6: Helsinki, Finland

2. **McLachlan R.** Investigation of the male prior to IVF and outcomes of the child. Asia Pacific Initiative on Reproduction. 2016, April 8 - 10: Jakarta, Indonesia

3. **Norman RJ, Alvino H, Hart R, Rombauts L, the LIGHT Investigators F.** A randomized double blind placebo controlled study of recombinant human growth hormone (r-HGH) on live birth rates in women who are poor responders. European Society of Human Reproduction and Embryology 32nd Annual Meeting; 2016, July 3 – 6: Helsinki, Finland.

4. **Rombauts L.** The endometrium in IVF: Endometrial markers of implantation. Asia Pacific Initiative on Reproduction. 2016, April 8 - 10: Jakarta, Indonesia.

5. **Shirlow RH, Healey M, Volovsky M, MacLachlan VB, Vollenhoven BJ.** The effect of intralipid on pregnancy rates in in vitro fertilization (IVF). American Society for Reproductive Medicine 72nd Scientific Congress; 2016, Oct 17- 19: Salt Lake City, USA.

6. **MacLachlan VB, Vollenhoven BJ.** Intrauterine human chorionic gonadotropin (HCG) infusion prior to embryo transfer (ET) may be detrimental to pregnancy rate. American Society for Reproductive Medicine 72nd Scientific Congress: 2016, Oct 17- 19; Salt Lake City, USA.

Poster presentations - National Conferences and Meetings

1. **Basnayake S, Schlink L, Martins W, MacLachlan V, Da Silva Costa F, Osianlis T, et al.** Differences in fetal growth and pregnancy outcomes between fresh and frozen embryo transfer. Annual Meeting of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists; 2016, Oct 16 – 19; Perth, Australia.

Books and Book Chapters

1. **Edgell TJ, Evans J, Rombauts L, Vollenhoven BJ, Salamonsen LA.** Assessing receptivity of the human endometrium to improve outcomes of fertility treatment. In: Kanzaki H, editor. Uterine Endometrial Function. Japan: Springer; 2016. p. 27-47.

MREF External Research Grants attracted in 2016

Professor Robert McLachlan

NHMRC Research grants

2016 - 2019
NHMRC Project Grant #1124606, Associate Investigator (AI). "The importance of the blood-testis barrier in human infertility"

2016 – 2021
NHMRC Project Grant #1120356, Associate Investigator (AI). "The genetic causes of male infertility"

Professor Luk Rombauts

NHMRC Research grants

2016 – 2021
NHMRC Project Grant #1120689, Associate Investigator (AI). "Facilitating endometrial receptivity to improve pregnancy outcomes"

2013 – 2016
NHMRC Project Grant #1042347, Associate Investigator (AI). "Banking on the future: Health care implications of reproductive tissue banks for people who store sperm, eggs, embryos and ovarian tissue before treatment for cancer."

Professor Beverley Vollenhoven

NHMRC Research grants

2014 - 2017
NHMRC Project Grant #1074342, Associate Investigator (AI). "Melatonin and Infertility"

2014 - 2017
ARC Linkage Grant
"Elucidating the increasing demand for genital cosmetic surgery among girls and women in Australia".

Monash Ultrasound for Women

ONGOING RESEARCH

Non-invasive prenatal testing with cell-free DNA for fetal trisomies 21, 18 and 13, in an ART population.

Dr Fabricio Costa[1], Andrew McLennan[2], Dr Simon Meagher[1], Dr Melody Menezes[1], Prof Jon Hyett[3].

[1]Monash Ultrasound for Women, Clayton;
[2]Sydney Ultrasound for Women, Burwood;
[3]Royal Prince Alfred Hospital, Sydney.

ART pregnancies have reduced first trimester combined screening (FTCS) PAPP-A levels leading to an increased likelihood of receiving a false-positive result. Non-invasive prenatal testing (NIPT) is a recently available advanced screening test which involves testing cell-free DNA (cfDNA) in the maternal plasma. These cells are released from the placenta (fetal genetic material) into the maternal circulation and this allows the detection of common autosomal trisomies (21, 18, and 13) with a high level of accuracy in singleton pregnancies. The objective of this study is to assess the performance of screening by NIPT for trisomies using a chromosome-selective sequencing method of cfDNA in maternal plasma obtained from an ART population undergoing routine screening at 11-13 weeks' gestation. A prospective chart review will be conducted to collect clinical data on patients who will have undergone combined FTCS and NIPT. From the 300 patients studied a high risk on FTCS is expected in 24-30 cases (~8-10%). We will compare the risk scores, between FTCS and NIPT.

The establishment of a normal range of embryonic heart rates in IVF pregnancies at seven weeks' gestation in an Australian population: embryonic heart rate as a determinant of first trimester loss

Presanna Sujenthiran[1], Dr Martha Finn[1], Dr Simon Meagher[1], Paul Lombardo[2].

[1]Monash Ultrasound for Women, Richmond;
[2]Dept. Medical Imaging and Radiation Sciences, Monash University.

ART births now account for ~3.6% of Australian births with almost 10,000 born each year. The 7 week ultrasound has become a definitive time to confirm a live intrauterine gestation for ART patients and it is therefore crucial to have established ultrasound parameters at this gestation. The boundary between normal and slow early embryonic heart rate (EHR) has not been well established in ART pregnancies. The study aims to establish a normal range of embryonic heart rates at 7 weeks gestation in ART singleton pregnancies as well as to analyse whether the EHR between 6W1D (i.e. 6 weeks and one day) and 7W6D in singleton ART pregnancies is useful in predicting the likelihood of first trimester loss. The range of EHRs will be evaluated to determine whether they form a normal distribution. The primary outcomes include successful first trimester pregnancy, confirmed by the standard 12 week ultrasound examination or miscarriage confirmed by ultrasound or medical documentation.

PeTALS: A longitudinal study exploring women's experiences following a prenatal diagnosis of fetal abnormality

Dr Melody Menezes[1], Prof Sylvia Metcalfe[2], Dr Jan Hodgson[2], Prof Jane Fisher[3], A/Prof Kerry Petersen[4], A/Prof Jane Halliday[2].

[1]Monash Ultrasound for Women, Richmond; [2]Murdoch Children's Research Institute, Parkville; [3]Jean Hailes Clinical Research Unit, Monash University, Clayton; [4]School of Law, La Trobe University, Melbourne.

Advances in genetic technologies are rapidly expanding the availability and accuracy of prenatal tests. In Australia, ~4% of babies are born with a fetal abnormality, many of which are diagnosed during pregnancy. Our multidisciplinary team will use a collaborative approach to understand how pregnant women are cared for following the diagnosis of a fetal abnormality, and to develop appropriate evidence-based models of supportive care. This study will be the first in Australia to investigate women's experiences of a prenatal diagnosis (PND) of fetal abnormality immediately following diagnosis. The study aims to:
(1) explore the psychosocial impact of a PND of fetal abnormality on women;
(2) identify the social and professional supports utilised and needed by women and
(3) describe the longer term outcomes for women who receive a diagnosis of a fetal abnormality.
The project will add to the existing knowledge in this under-researched field and contribute directly to improving the social and clinical care of women together with the education of the health professionals who care for them.

Reproducibility of three-dimensional ultrasound of the junctional zone in myometrial pathology and their correlation with pregnancy rates

Dr Lufee Wong[1,2], A/Prof Fabricio Costa[1,2], Dr Simon Meagher[1]

[1]Monash Ultrasound for Women, Richmond; [2]Monash Medical Centre, Clayton

During pregnancy, the endometrial-myometrial junction, or junctional zone (JZ), is fundamental to the process of implantation and placentation. Consequently, any myometrial disorders, such as adenomyosis, can disrupt the process, leading to infertility and various pregnancy complications. While magnetic resonance imaging (MRI) can be used in the assessment of the JZ, it is not readily available, expensive and can be claustrophobic for some patients. Three-dimensional (3D) ultrasound has made it possible to assess minor changes in the JZ. A consensus statement in 2015 on the classification system of myometrial disorders aims to assess the JZ using standardized nomenclature. This study aims to evaluate the reproducibility of this evaluation of the JZ using 3D-ultrasound, as well as the correlation of the JZ changes with pregnancy rates. Being able to accurately diagnose adenomyosis will help in the diagnosis and counseling of patients with infertility before undergoing IVF cycles. Furthermore, recent studies have identified that small non-coding RNA, microRNA (miR), are differentially expressed in human endometrium across the menstrual cycle suggesting they are hormonally controlled. Uterine miR expression levels are altered in a number of uterine disorders and a recent study demonstrated that miR levels in human endometrium correlate with serum levels in women with primary infertility. We propose that similarly miR levels in serum may reflect alterations in the JZ and may be useful in the diagnosis of adenomyosis in conjunction with 3D-ultrasound.

Monash Ultrasound for Women (continued)

Contributions to Scientific Literature

Peer Reviewed Journal Articles/Publications

1. **Chen Q, Wang Y, Zhao M, Hyett J, da Silva Costa F, Nie G.** Serum levels of GDF15 are reduced in preeclampsia and the reduction is more profound in late-onset than early-onset cases. Cytokine. 2016 Jul; 83: 226-30.

2. **E Holanda Moura SB, Park F, Murthi P, Martins WP, Kane SC, Williams P et al.** TNF-R1 as a first trimester marker for prediction of pre-eclampsia. J Matern Fetal Neonatal Med. 2016 Mar; 29(6): 897-907.

3. **E Holanda Moura SB, Praciano PC, Gurgel Alves JA, Martins WP, Arauko JE, Kane SC et al.** Renal interlobar vein impedance index as a first-trimester marker does not predict hypertensive disorders of pregnancy. J Ultrasound Med. 2016 Dec; 35(12): 2641-2648.

4. **Ghi T, Sotiriadis A, Calda P, Da Silva Costa F, Raine-Fenning N, Alfirevic Z, et al.** ISUOG Practice Guidelines: invasive procedures for prenatal diagnosis. Ultrasound in Obstetrics & Gynecology. 2016 Aug 1; 48(2):256-68.

5. **Hodgson J, Pitt P, Metcalfe S, Halliday J, Menezes M, Fisher J, et al.** Experiences of prenatal diagnosis and decision-making about termination of pregnancy: A qualitative study. Aust N Z J Obstet Gynaecol. 2016 Dec; 56(6): 605-613.

6. **Hui L, Teoh M, da Silva Costa F, Ramsay P, Palma-Dias R, Richmond Z, et al.** Opinion: Clinical implementation of cell-free DNA-based aneuploidy screening: perspectives from a national audit. Ultrasound obstet Gynecol. 2015; 45: 10-15. *Not included in 2015 MREF Annual report*

7. **Júnior EA, Meagher S, Gonçalves LF.** Fetal Malformations Detected by Three-dimensional Ultrasound. Advanced Topics on Three-Dimensional Ultrasound in Obstetrics and Gynecology. 2016 May; 6:191.

8. **Kane SC, Brennecke SP, da Silva Costa F.** Ophthalmic artery Doppler analysis: a window into the cerebrovasculature of women with pre-eclampsia. Ultrasound Obstet Gynecol. 2016 Dec; 49(1): 15 – 21.

9. **Kane SC, Willats E, Bezerra Maia e Holanda Moura S, Hyett J, da Silva Costa F.** Pre-Implantation genetic screening techniques: Implications for Clinical Prenatal Diagnosis. Fetal Diagn Ther. 2016 Sept 29.

10. **McLennan A, Palma-Dias R, da Silva Costa F, Meagher S, Nisbet DL, Scott F.** Noninvasive prenatal testing in routine clinical practice - an audit of NIPT and combined first-trimester screening in an unselected Australian population. Aust N Z J Obstet Gynaecol. 2016 Feb;56(1):22-8.

11. **Praciano De Sousa PC, Gurgel Alves JA, Bezerra Maia E Holanda Moura S, Arauko JE, Martins WP, et al.** Brachial artery flow mediated dilation and pulsatility index change as independent predictors for hypertensive disorders in the second trimester or pregnancy. Eur J Obstet Gynecol Reprod Biol. 2016 May; 200: 94-97.

12. **Tonni G, Castigliego AP, Grisolia G, Lituania M, Meagher S, Da Silva Costa F, et al.** Three- dimensional ultrasonography by means of HDlive rendering in the first trimiester of pregnancy: A pictorial review. J Turk Ger Gynecol Assoc. 2016 Jan; 17(2): 110-119.

13. **Wang Y, Li Y, Hyett K, da Silva Costa F, Nie G.** HtrA3 isoform-specific ELISAs for early detection of preeclampsia. J Biomol Screen. 2016 Dec 8.

14. **Wong L, White N, Ramkrishna J, Arauio JE, Meagher S, da Silva Costa F.** Three-dimentional imaging of the uterus: The value of the coronal plane. World J Radiol. 2015 Dec; 7(12): 484-493. *Not included in 2015 MREF Annual report*

Presentations - International Conferences and Meetings

1. **da Silva Costa F.** Interlobar renal vein Doppler as a first trimester predictor of pre-eclampsia. Second International Congress on Maternal Hemodynamics; 2016, May 12 - 14; Rome, Italy. **Awarded "Best oral presentation".*

2. **Menezes M, McLennan A, Scott F, Palma-Dias R, Kornman L, da Silva Costa F.** OP08. 05: Factors affecting fetal fraction in 5,103 cases of a mixed Australian population. 26th Congress on Ultrasound in Obstetrics & Gynecology. 2016 Sep 25-28; Rome, Italy.

Presentations - National Conferences and Meetings

Poster presentations

1. **Bezerra S, Praciano P, Gurgel Alves JA, Martins WP, Silva Costa F.** EP17.09: Reference values of maternal renal interlobar venous Doppler parameters in the first trimester of normal pregnancy. 26th Congress on Ultrasound in Obstetrics & Gynecology. 2016 Sep 25-28; Rome, Italy

2. **Bezerra S, Praciano P, Gurgel Alves JA, Martins WP, Silva Costa F.** EP15. 20: Predicting small-for-gestational age newborns in the first trimester of pregnancy using maternal renal interlobar vein impedance (RIVI). 26th Congress on Ultrasound in Obstetrics & Gynecology. 2016 Sep 25-28; Rome, Italy

3. **Santos NS, Gurgel Alves JA, Bezerra S, Silva Costa F.** EP17. 18: Comparison of perinatal outcomes in early-and late-onset pre-eclampsia. 26th Congress on Ultrasound in Obstetrics & Gynecology. 2016 Sep 25-28; Rome, Italy.

Repromed

COMPLETED PROJECTS

Prof Kelton Tremellen
Repromed, Dulwich and Flinders University, Adelaide

Dr Deirdre Zander-Fox
Repromed, Dulwich and University of Adelaide, Adelaide

Prof Michelle Lane
The University of Adelaide, Adelaide and Monash IVF, Clayton

Dr Hamish Hamilton
Repromed, Dulwich, Adelaide

Major advances in IVF technology have led to significant improvements in pregnancy rates and SET usage. Historically, pregnancy rates have increased with greater numbers of eggs collected, therefore superovulation procedures were designed to obtain 10-15 eggs however recent modelling from our laboratory as well as studies in Europe and the USA have shown that pregnancy rates in young women now plateau at 4-5 eggs. Furthermore, there is evidence that high dose stimulation is associated with an increase in poor oocyte quality and impaired endometrial competence. Due to this, lower stimulation protocols have been developed which have the benefit of reducing OHSS risk, increasing egg and embryo quality while maintaining equivocal pregnancy rates. In addition due to the low oocyte number, egg retrieval under local anesthetic is also a possibility.

As such we initiated the MINIVA trail which is a pilot case-matched study to establish the efficacy and patient feedback to low intensity IVF. This study assessed the use of low stimulation regime coupled with egg retrieval under local anesthetic and was compared to a case matched group. The primary outcome for this trial is clinical pregnancy rate as determined by viable fetal heart beat at 8 week scan with secondary outcomes including fertilisation rates, embryo quality and utilization, pregnancy rates, cumulative pregnancy rates, cycle cancellation rates and pain tolerance to local anesthetic. This study has been completed and is being written up for submission.

ONGOING PROJECTS

The impact of being overweight and obesity in men with antioxidant consumption on sperm quality, embryo development, pregnancy rates and live birth outcome

Prof Michelle Lane
The University of Adelaide, Adelaide and Monash IVF, Clayton

Dr Deirdre Zander-Fox
Repromed, Dulwich and University of Adelaide, Adelaide

Helana Shehadeh
The University of Adelaide, Adelaide

Dr Tod Fullston
The University of Adelaide, Adelaide

Male obesity rates are increasing at an alarming rate, and concomitantly the degree of obese reproductive aged men is rapidly increasing worldwide, highlighting their need for assisted reproductive technologies. Recent clinical studies have shown a correlation between dietary antioxidant intake in normal weight males and improvement of sperm function, primarily due to a reduction in oxidative stress within sperm. However, whether antioxidant therapy could aid in the reduction of oxidative stress levels and consequent oxidative DNA damage in sperm and its effects on sperm quality and function in obese men remains unknown. This study will assess the impact of antioxidant treatment on sperm quality, sperm function measures and its consequences in a patient's assisted reproductive cycle. The outcomes of this project will provide evidence to guide future human clinical trials in understanding the consequences of environmental factors such as obesity that impact embryo, fetal and child health and therefore contribute to public health policy.

Repromed (continued)

Contributions to Scientific Literature

Peer Reviewed Journal Articles/Publications

1. **Fullston T, Ohlsson-Teague EMC, Print CG, Sandeman LY, Lane M.** Sperm microRNA content is altered in a mouse model of male obesity, but the same suite of microRNAs are not altered in Offspring's sperm. PLos One. 2016 Nov 4.

2. **McPherson NO, Owens JA, Fullston T, Lane M.** Preconception diet or exercise intervention in obese fathers normalizes sperm microRNA profile and metabolic syndrome in female offspring. Am J Physiol Endocinol Metab. 2015 Feb; 308: 805-821. *Not included in 2015 MREF Annual report*

3. **McPherson NO, Fullston T, Kang WX, Sandeman LY, Corbett MA, Owens JA, et al.** Paternal under-nutrition programs metabolic syndrome in offspring which can be reversed by antioxidant/vitamin food fortification in fathers. Sci Rep. 2016; 6: 27010.

4. **Sharkey DJ, Tremellen KP, Briggs NE, Dekker GA, Robertson SA.** Seminal plasma transforming growth factor-β, activin A and follistatin fluctuate within men over time. Hum Reprod. 2016 Oct; 31(10):2183-91.

5. **Tremellen K, Everingham S.** For love or money? Australian attitudes to financially compensated (commercial) surrogacy. Aust N Z J Obstet Gynaecol. 2016 May; 56(6):558-563.

6. **Tremellen K, Pearce K, Zander-Fox D.** Increased miscarriage of euploid pregnancies in obese women undergoing cryopreserved embryo transfer. Reprod BioMed online. 2016 Oct 17.

Presentations - National Conferences and Meetings

1. **Krishna P, Lane M, Fullston T, Zander-Fox D.** The impact of royal jelly supplementation in embryo culture media on embryo development and quality. SIRT Annual Meeting; 2016 April 30 – May 1. Adelaide, Australia.

2. **Pacella-Ince L, Grant W, Zander-Fox D.** Detection of Robertsonian Translocations using Next Generation Sequencing. SIRT Annual Meeting; 2016 April 30 – May 1. Adelaide, Australia. *Won "Established Scientist Award"*

3. **Shehadeh H, Fullston T, Zander-Fox D, Lane M.** The impact of antioxidant supplementation in overweight and obese men on sperm quality, sperm function, embryo development, and pregnancy rates. SIRT Annual Meeting; 2016 April 30 – May 1. Adelaide, Australia. *Won "Young Scientist Award"*

Presentations - International Conferences and Meetings

1. **Tremellen K.** You are what you eat; mechanisms by which the gut can effect reproduction. The 10th Biennial Conference of the Association of Clinical Embryologists; 2016, Jan 6; Newcastle, UK.

2. **Dr Deirdre Zander-fox** was invited to the 2016 Reproductive Symposia, Tokyo and Osaka, Japan, to speak on:

    a. PGS and PGD for the majority of patients: Setting up and managing genetic screening in-house
    b. Managing an IVF lab with superior results: the importance of using an unbroken chain of high quality products.

Books and Book Chapters

1. **Fullston T, Shehadeh H, Schjenken J, McPherson N, Robertson S, Zander-Fox D, Lane M.**
Paternal Obesity and Programming of Offspring Health. In: Green LR, Hester RL, editor. Obesity: Intergenerational Programming and Consequences. New York: Springer; 2016. p. 3-33.

Supporting the Monash IVF Group Research and Education Foundation

The Monash IVF Group Research and Education Foundation recognises the benefits of conducting original research and of undertaking dynamic educational programs to maintain its leading position in reproductive medicine, and to fulfill its social duty to improve health care.

- The MREF acknowledges with appreciation the support provided by MSD, Merck Serono Australia and Ferring Pharmaceuticals

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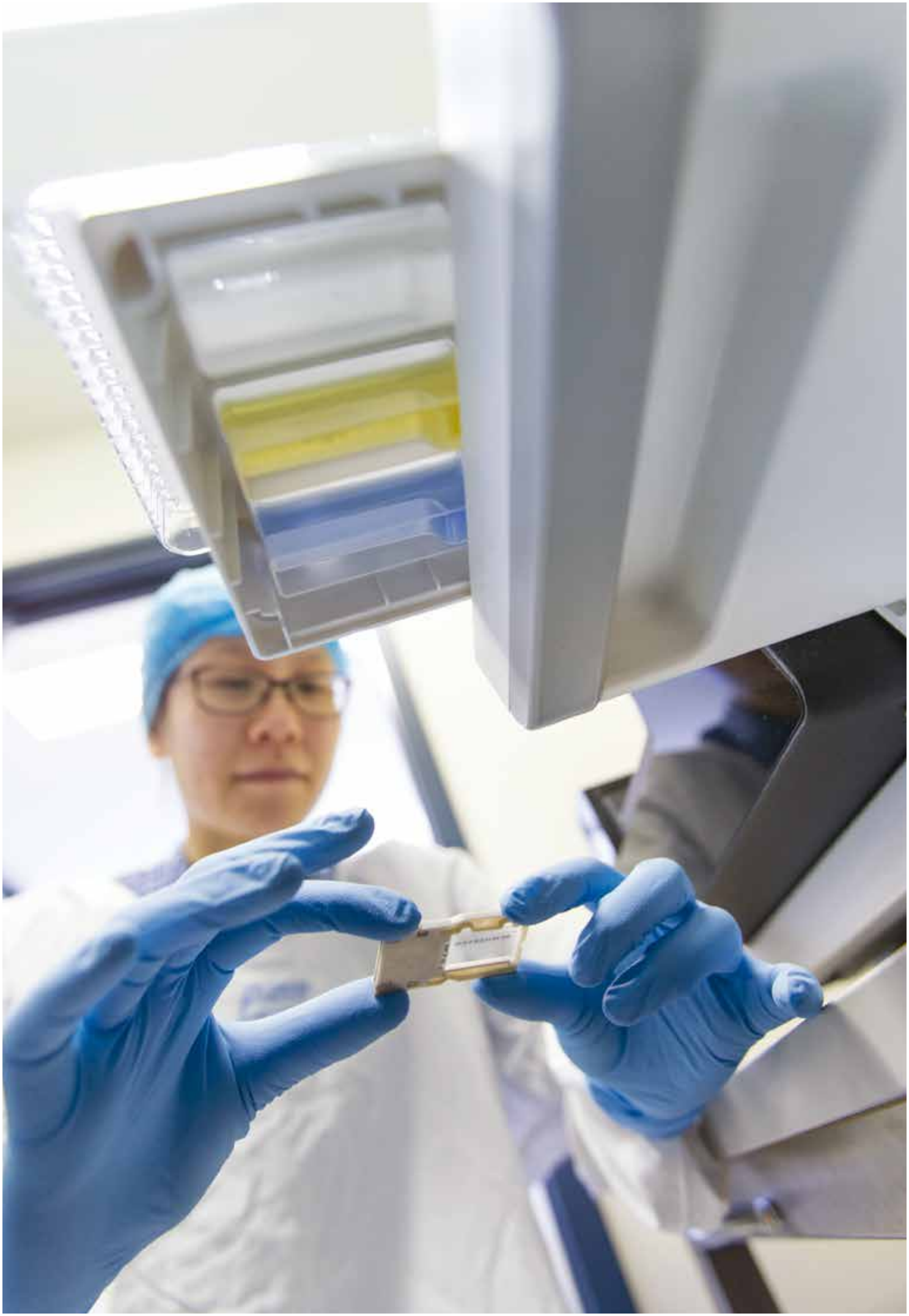

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More information

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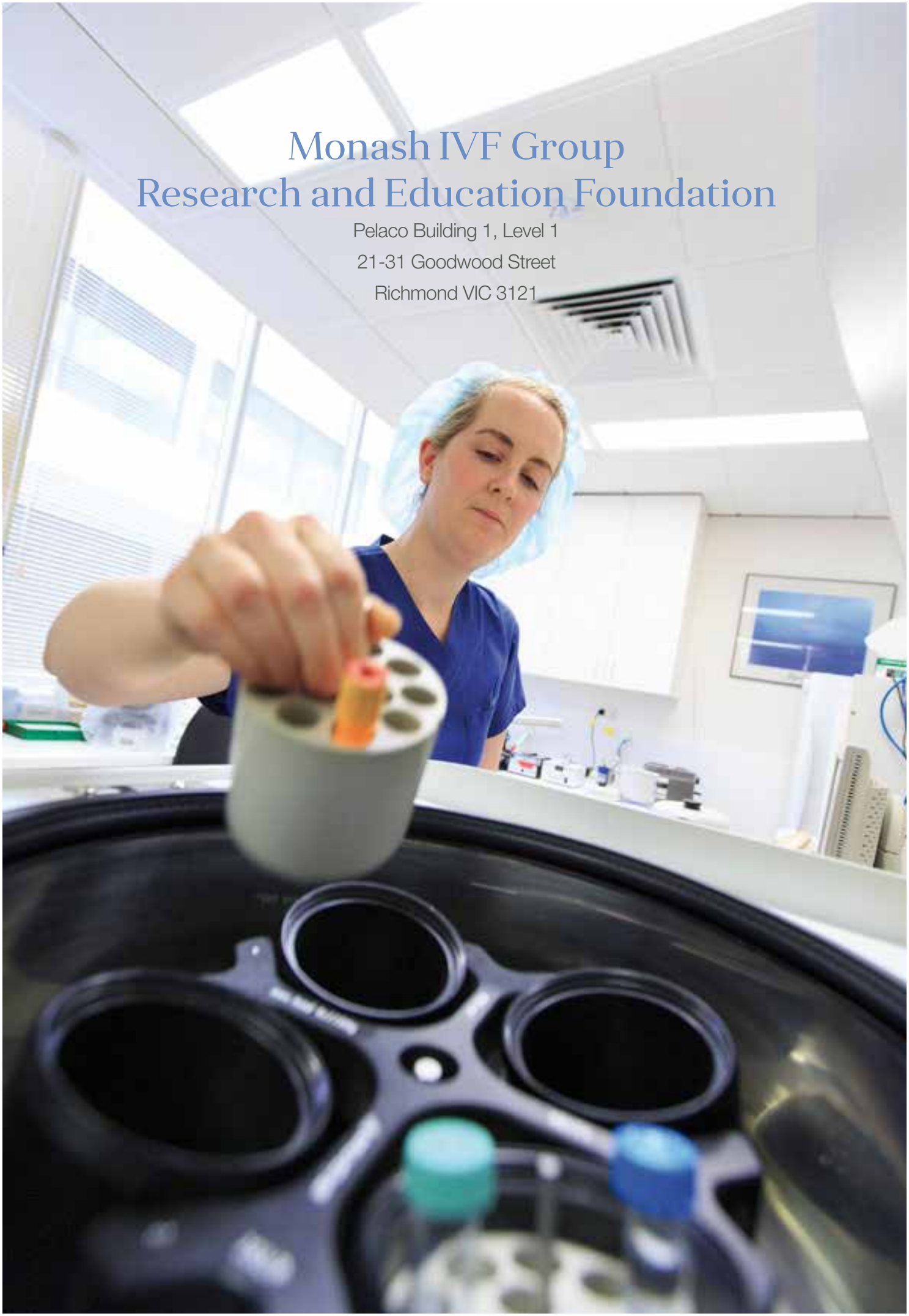

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